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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Madden et al.
Application No.	:	09/896,811
Filed	:	June 29, 2001
For	:	LIPOSOMAL CAMPTOTHECINS AND USES THEREOF
Examiner	:	Clinton T. Ostrup
Art Unit	:	1614
Docket No.	:	480208.407

CTO
10/30/03

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF SEAN SEMPLE, M Sc

PURSUANT TO 37 C.F.R. §1.132

I, Sean Semple, declare as follows:

1. I am a Senior Scientist at Inex Pharmaceuticals, the assignee of the above-identified application and a co-inventor of the subject matter disclosed therein.

2. I am familiar with the content of this application, and I have reviewed the Office Action mailed April 7, 2003 and the prior art references cited therein. I have compared the experimental results described in the cited prior art references to the experimental results described in this application, and I conclude that the compositions and methods described and claimed in this application offer unexpectedly superior results over the prior art. The bases for this conclusion are summarized below.

3. The liposomal topotecan compositions described and claimed in the present application, comprising sphingomyelin and cholesterol, exhibited markedly

increased efficacy as compared to free topotecan, in a variety of different experimental models. These liposomal topotecan compositions exhibited efficacy at dosages that have not previously been demonstrated to be efficacious using either free topotecan or the liposomal camptothecin compositions described in Slater *et al.*

4. In studies using the CT-26 murine colon carcinoma model, when administered at a dosage of 2 mg/kg, the liposomal topotecan compositions of the present application exhibited a 20-fold increase in potency as compared to free topotecan (page 20, lines 5-8).

5. In studies using the MX-1 human breast carcinoma model, when administered at 2 mg/kg, these liposomal topotecan compositions exhibited an optimal Treated/Control (%T/C) ratio value of 8%, which compared favorable to the optimal %T/C value of 24%, which was observed using 40 mg/kg of free topotecan, the highest dose tested (page 20, lines 25-32). For %T/C, low or negative values indicate tumor growth inhibition or tumor regression, respectively.

6. In multiple dose studies in the MX-1 human breast carcinoma model, liposomal topotecan displayed significant efficacy at dosages as low as 0.5 mg/kg and 1.25 mg/kg, with corresponding optimal %T/C values of -15% and -100%, respectively, while free topotecan exhibited minimal activity at 1.25 mg/kg, with a corresponding optimal %T/C value of 55%, which is greater than the minimum acceptable limit of <42% for advancing a drug further in development established in NCI guidelines (page 22, lines 6-11). Treatments described in the instant application were administered on either a q7dx3 or a q4dx3 dosing schedule.

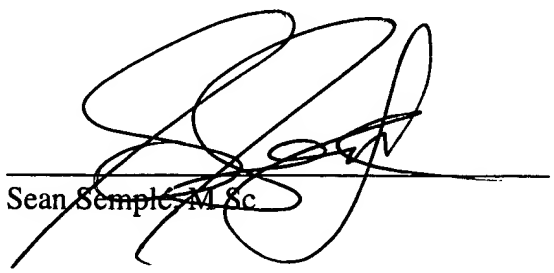
7. In contrast to the above studies, Slater *et al.* provides no evidence that their described liposomal topotecan compositions were efficacious at dosages below 2 mg/kg. Furthermore, the data presented in Slater *et al.* regarding their liposomal topotecan compositions indicates that dosages as high as 2 mg/kg are markedly less

efficacious than higher dosages of 5 mg/kg or 8 mg/kg (Table 6 and column 18, lines 7-11). All treatments described in Slater *et al.* were administered as i.v. bolus injections weekly on days 9, 16 and 23.

8. In addition, the liposomal topotecan compositions of the instant application exhibited increased efficacy as compared to the liposomal topotecan compositions described in the cited prior art. When used at similar dosages, the liposomal topotecan compositions of the instant application showed increased efficacy as compared to the liposomal topotecan compositions described in the cited prior art. For example, in one multiple dose study described in Slater *et al.* employing a human xenograft HT-29 tumor model, the %T/C values for liposome-entrapped topotecan at dosages of 2 mg/kg and 5 mg/kg ranged from 5.6% to 19.5% (Table 7), while in multiple dose studies described in the instant application employing human xenograft tumor models (MX-1 and LX-1), the %T/C value for dosages of 2.5 and 5 mg/kg were both -100% in the MX-1 model (page 22, lines 9-11) and 3% and -5%, respectively, in the LX-1 model.

I hereby declare that all statements made herein are, to my own knowledge, true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

Date OCT. 6, 2003



Sean Semple, M.Sc.